Synthesis of Carbocyclic Analogues of D-Glucosamine and L-Idosamine from D-Glucosamine

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Derivatives of pseudo-D-glucosamine and pseudo-L-idosamine have been prepared from the chiral cyclohexanone (**1**) by a short sequence, including methoxy-methylenation or methylenation, followed by stereoselective oxymercuration or hydroboration, respectively of the resulting vinyl ether (**2**) and exocyclic methylene (**3**).

There has been recently much interest in the chemistry and biochemistry of 'carbocyclic' sugars, in which the furanose[1—3] and pyranose[4,5] oxygen atoms have been replaced by a methylene group. Such alteration might confer interesting physiological properties on the pseudo-sugars, by virtue of their structural resemblance to the parent carbohydrates.

As part of a larger research programme, we describe in this communication† the stereocontrolled synthesis of some derivatives of pseudo-α-D-glucosamine and pseudo-β-L-idosam-

† All new compounds exhibited spectroscopic and analytical data consistent with the assigned structure.

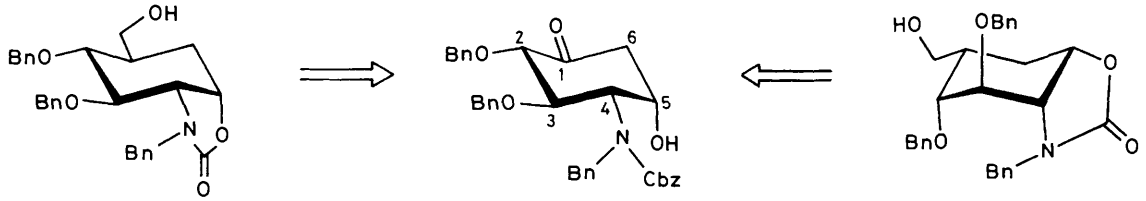
ine. Neutral, 'pseudo-sugars' have been described, mainly as racemic mixtures, which have been resolved in some instances.[6] The enantioselective synthesis of the title compounds has not been reported previously. The synthesis of some molecules related to pseudo-D-glucosamine by a completely different synthetic strategy was disclosed recently.[5,7]

Retrosynthetic analysis of the title molecules suggested that they could be synthesised from a chiral cyclohexanone (**1**). The latter possesses the substitution pattern and the chiral centres (C-2, C-3, C-4, and C-5) of the target molecules as shown (Scheme 1). Since no corresponding studies have been conducted in the past with such highly functionalised cyclohexanones, it was not possible to predict the overall efficiency and stereoselectivity of the transformations proposed.

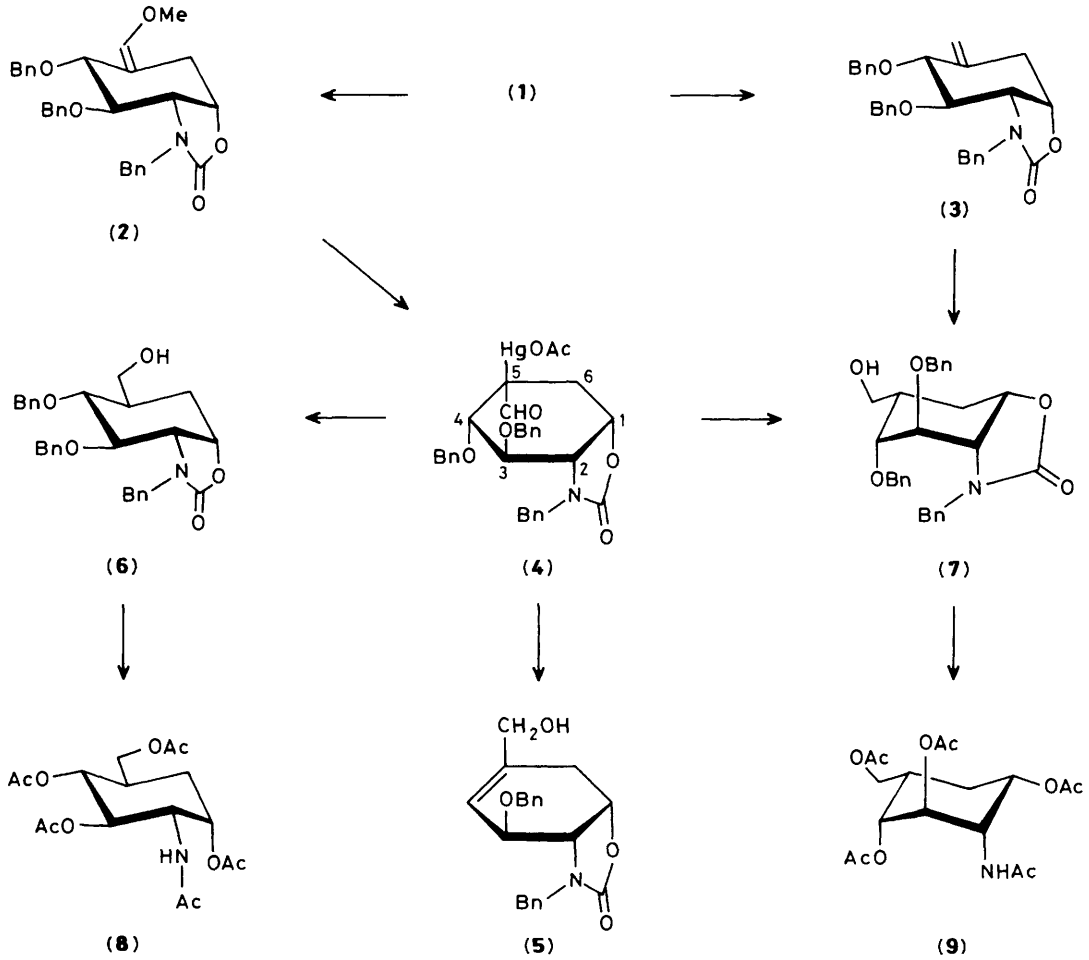
The substituted cyclohexanone (**1**) is readily available[8] from D-glucosamine and was therefore the starting material of choice. The first problem of the synthesis was the preparation of the vinyl ether (**2**) and exocyclic alkene (**3**) from the cyclohexanone (**1**). It was of general synthetic interest to ascertain whether such a process would be operative with the highly oxygenated cyclic ketone (**1**), which is particularly prone to β-elimination and aromatisation.

Treatment of (**1**) with Wittig reagents, employing methoxymethylenetriphenylphosphorane (4 equiv. in dimethoxyethane) and methylenetriphenylphosphorane (4 equiv. in dimethoxyethane) at −5 °C, followed by warming to 10 °C over 45 min, afforded the syrupy vinyl ether (**2**) (60%), $[\alpha]_D^{25}$ −12° (*c* 1, $CHCl_3$) and the crystalline exocyclic alkene (**3**) (67%), m.p. 87—88 °C, $[\alpha]_D^{25}$ −48.7° (*c* 1.6, $CHCl_3$), respectively.

Concomitant intramolecular attack by the alkoxide anion at C-5 on the neighbouring benzyloxycarbonyl group leading to the oxazolidones (**2**) and (**3**) was evident from the analytical



Scheme 1. Bn = CH_2Ph; Cbz = CO_2CH_2Ph.



and n.m.r. data. Interestingly, in the case of the vinyl ether only one geometrical isomer was formed. Since in the next step the double bond was to be destroyed no attempt was made to determine its geometry.

The remaining problem in the present study was the conversion of the alkenes (**2**) and (**3**) into the desired carbocyclic derivatives of D-glucosamine and L-idosamine. We focused our attention on oxymercuration and hydroboration of (**2**) and (**3**), respectively.

Initial attempts to convert the vinyl ether (**2**) into a pseudo-sugar [using mercury(II) nitrate in acetonitrile–water, followed by successive reaction with aqueous potassium iodide and sodium borohydride] afforded exclusively the unsaturated alcohol (**5**) in 83% yield, m.p. 86—87 °C, $[\alpha]_D^{25}$ +61° (*c* 1.15, $CHCl_3$).

However, when the sequence of reactions was repeated employing mercury(II) acetate, a mixture of two products was isolated in 60% yield. They were separated by silica gel high pressure liquid chromatography. The structure of the diastereoisomers (ratio 8:2) was rigorously established.

The major component was shown to be (**6**), $[\alpha]_D^{25}$ +10.6° (*c* 1.0, $CHCl_3$), and the minor diastereoisomer was identified as (7), $[\alpha]_D^{25}$ −2.5° (*c* 1.0, $CHCl_3$). The major product of this process was clearly the carbocyclic analogue (**6**) of D-glucosamine.

Because of our interest in the synthesis of the pseudo-L-idosamine, as well as a desire to confirm the above structural assignments, we studied the hydroboration of the exocyclic alkene (**3**).

Hydroboration of (**3**) with diborane in tetrahydrofuran, followed by oxidative work-up of the resulting organoborane, yielded (7) as the only detectable diastereoisomer in 60% yield. The spectral data of this product (i.r., ^1H and ^{13}C n.m.r., and mass) and its chromatographic behaviour (t.l.c. and h.p.l.c.) were identical with those of (7) prepared from the vinyl ether (**2**).

The remarkable preference for the β-face hydroboration of (**3**), which determines the stereochemistry of the final product (7) is undoubtedly due to the presence of the bulky oxazolidone ring, which directs the attack of borane (BH_3) from the less shielded convex face.

In analogy to the hydroboration, it seems likely that the oxymercuration of the vinyl ether (**2**) also occurs from the β-face to give (**4**). However, since the reduction of the carbon–mercury bond in (**4**) by borohydride proceeds by a radical pathway,[9] epimerisation at C-5 is possible, producing the two corresponding alcohols (**6**) and (7) in a ratio of 8:2 respectively, the more stable alcohol being preponderant.

Finally both alcohols (**6**) and (7) were treated with sodium hydroxide in ethanol (10%, reflux over 6 h), hydrogenolysed, and peracetylated to yield the desired crystalline (**8**) (65%), m.p. 74—75 °C, $[\alpha]_D^{25}$ +68° (*c* 0.7, $CHCl_3$), and (**9**) (63%), $[\alpha]_D^{25}$ +19.5° (*c* 0.9, $CHCl_3$), isolated as a foam.

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